THE RELATIONSHIP OF ADRENAL CORTICAL ACTIVITY TO IMMUNE RESPONSES*

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ONE year ago it would have been thought odd to consider the treatment of certain of the diseases discussed tonight with steroids of the adrenal gland. However, these diseases have long been thought to be related to immune processes[1-3] and the study of the effect of the adrenals on immunity has an enormous bibliography.[4, 5]

It is well known that patients with Addison's disease appear to be particularly vulnerable to relatively innocuous infections. By adrenalectomy, animals are rendered more susceptible to many noxious stimuli. Therefore, it is not surprising to find reports that such animals are more readily thrown into anaphylactic shock than are normal animals, either by antigen antibody reactions[6, 7] or histamine injections.[8] The lack of the adrenalin secreting mechanism that accompanied the loss of the adrenal certainly played a part in this altered susceptibility, but the cortex also appeared to be of significance, as suggested by substitution therapy experiments. In 1935, Wolfram and Zwemer[6] observed that the administration of adrenal cortical extract to adrenalectomized animals resulted in greater resistance to anaphylactic shock. This finding has been confirmed in many animal species, the most recent being the prevention of a type of anaphylactic death in mice by Dougherty.[9] Such studies emphasize the vulnerability of adrenalectomized animals to noxious stimuli and the value of replacement therapy, as Dr. Russell mentioned earlier this evening, but are too complex to permit an appraisal of specific effects on immune reactions. Whether the adrenal hormones influence the union of antigen with antibody, or influence the resulting reaction of the tissues might be studied more profitably in intact animals. They present fewer variables than do adrenalectomized animals and clinical studies suggest that the administration of cortisone

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TABLE I—EFFECT OF ACTH ON THE ARTHUS REACTION PASSIVELY INDUCED WITH KNOWN AMOUNTS OF ANTI-OVALBUMIN NITROGEN (AbN) AND CRYSTALLINE EGG ALBUMIN.

Number of reactions of different severity related to total number of reactions in each group

Rabbits

	0.2 mg AbN		0.02 mg AbN			
	++++	+++	++	+	±	0
Control	9/10	1/10	1/10	6/10	1/10	2/10
ACTH:						
2 mg/day for 5 days	4/6	2/6		5/6		1/6
6 mg 6 hrs. before	6/6			5/6	1/6	
8 mg/kilo/day in 4 doses	4/4			2/4	2/4	

Guinea Pigs

	0.2 mg AbN		0.01 mg AbN			
	++++	+++	+++	++	+	0
Control	5/6	1/6		3/6	3/6	
ACTH:						
1 mg/day for 5 days	4/4			2/4	1/4	1/4
3 mg 6 hrs. before	4/4		1/4	2/4	1/4	
32 mg/kilo/day in 4 doses	2/3	1/3		3/3		

may have an effect on immune reactions even in the presence of intact adrenal glands. Employing Kabat's quantitative technique for the induction of anaphylaxis,[10] we have found no alteration from normal susceptibility to anaphylactic shock in intact guinea pigs treated with ACTH.* Using horse serum, which does not lend itself to the quantitative method, Leger, Leith and Rose[11] have reported a similar lack of effect of ACTH on anaphylaxis.

Anaphylaxis is not, perhaps, the best system to study as an example of an allergic reaction. Many investigators have looked upon rheumatic fever and to some extent rheumatoid arthritis as diseases that may perhaps be induced by antigen-antibody reactions of the *necrotizing* variety. A simple system by which the degree of tissue damage can be produced quantitatively in an expected way was established in studies with

* Adrenocorticotropic hormone was kindly furnished for these studies by Dr. Edwin E. Hays, Director, Biochemical Research, Armour & Company.

Kabat.[12] This reaction is the familiar Arthus reaction that results from the union of certain antigens with their antibodies in tissues. Rabbits and guinea pigs were sensitized passively with known amounts of rabbit anti-ovalbumin nitrogen locally; either 0.22 mg. of antibody nitrogen (AbN) to produce a severe reaction, or 0.02 mg. AbN for a minimal reaction. Subsequently a challenging injection of antigen (four times recrystallized hen ovalbumin) was administered intravenously. The site of the antibody injections became inflamed and were measured according to previous criteria.[12, 13] It is apparent from Table I that animals pretreated with ACTH in various doses did not have any appreciable difference from control animals in the severity of Arthus reactions, at either the severe or mild levels.

Another allergic system, nephrotoxic nephritis, has been studied in relation to cortisone administration by Knowlton and her coworkers.[14] No appreciable difference was noted in the nephritis when cortisone was administered either before or concurrently with the nephrotoxic antibody. Necrotizing allergic reactions in humans have been studied by several investigators. In our experience, skin sensitivity to tuberculin or to a streptococcal nucleoprotein fraction did not appear to be altered in patients receiving ACTH or cortisone in doses causing a remission of their underlying disease process. However, in one individual receiving very large amounts of ACTH there did occur an inhibition of the tuberculin reaction. This patient also developed widespread acne, hirsutism and the facies of Cushing's syndrome. The failure to elicit a tuberculin reaction here may be related more to the effect on connective tissue discussed by Dr. Ragan[15] than to an inhibition of an immune reaction.

At the present time, it appears that cortisone and ACTH do not alter the union of antigen with antibody. What effect, if any, might they have on antibody formation? There is much conflicting literature concerning the role of the adrenal cortical gland in the production of antibodies.[4] Perhaps most provocative was the report that under conditions of non-specific stress, or adrenal cortical activity, antibodies were increased in the circulation, apparently released from lymphocytes.[16] It appeared worthwhile to study this so-called anamnestic response with the more exacting disciplines of immunochemistry as introduced by Dr. Heidelberger,[17, 18] namely, the use of a single purified antigen and an analytical chemical technique for the determination of its antibody.

Accordingly with Drs. LeMay and Kabat,[19] a series of rabbits were

TABLE II*—THE EFFECT OF ADRENOCORTICOTROPHIC HORMONE ON THE ANTIBODY CONTENT OF SERUM, THE AMOUNT OF TOTAL WHITE CELLS AND OF LYMPHOCYTES. 25 MG. ADRENOCORTICOTROPHIC HORMONE GIVEN ON NOV. 13TH

	Rabbit	August 1947	November 11	November 13		48 hrs. after stimulus
				6 hrs. after stimulus	12 hrs. after stimulus	
C3	WBC		13,250	16,250	12,150	7,700
	Lymph		9,500	2,700	4,130	5,080
	μg. AbN/ml	170	2	0	0	0
S1	WBC		10,700	3,600		
	Lymph		6,250	685		
	μg. AbN/ml	180	10	3		
S3	WBC		10,550	15,000	5,190	
	Lymph		5,180	2,500	1,500	
	μg. AbN/ml	1,060	28	20	15	
SM	WBC		13,350	10,450	7,900	9,700
	Lymph		7,480	3,350	3,550	5,920
	μg. AbN/ml	320	18	11	12	11
X6	WBC		28,650	17,600	28,600	12,000
	Lymph		11,750	5,450	12,600	7,550
	μg. AbN/ml	210	12	10	10	10
N2	WBC		11,600	11,700	13,900	4,300
	Lymph		8,020	1,650	3,600	1,115
	μg. AbN/ml	63	0	0	0	0

* Reproduced from J. Immunol., 1949, 61, with permission of the authors,[19] the J. Immunol., and the Williams & Wilkins Co., publisher.

immunized with crystalline egg albumin and allowed to rest for three months. The antibody content of the serum at the end of the course of immunization is shown in the first column of Table II. After three months of rest, the amount of antibody nitrogen per ml of serum diminished appreciably to from zero to twenty-eight gamma. A single large dose of adrenocorticotrophic hormone was given. Although a fall in lymphocytes occurred, as indicated by the data in Table II, no increase in antibody was found. Indeed, if anything, a slight indication of a decrease was found in these animals as well as in a group given X-ray treatment instead of the ACTH. Drs. Eisen, Stoerk and their group,[20] also employing quantitative immunochemical methods, likewise reported that adrenal cortical extract failed to enhance circulating antibody.

Clinically, it is apparent that in several of the diseases associated with hyperglobulinemia a fall in the level of serum globulin is usually noted when cortisone or ACTH is administered. This appears to be in con-

tradistinction to the increase in globulin or in antibodies reported to occur in animals immunized concomitantly with the administration of cortical extract.[21]

With Drs. Bjørneboe and Stoerk, a small number of rabbits were immunized to pneumococcus by a technique which results in the rapid production of large amounts of globulin,[22] comparable in degree to that found in clinical hyperglobulinemia. In these animals, however, the increase in globulin is measurable as specific antibody globulin. One group of animals was given ACTH in a very small dose per day (between 0.5 and 1.0 mg.). Preliminary observations give evidence of an inhibition or diminution of antibody. Despite some overlap in individual titers, the mean antibody level of animals treated with ACTH was about half of that of the control group at the end of fourteen days and at the end of twenty-eight days. Dr. Stoerk[23] has independently studied the effect of cortisone on antibody production with results indicative of the same effect.

It is possible that this effect on antibody production may be one of the mechanisms by which cortisone alleviates rheumatoid arthritis and associated conditions, but this is highly speculative at the present time. The dramatic effects of cortisone on certain known allergic conditions such as hay fever and asthma, as recently reported[24] and as seen incidentally in certain of Dr. Ragan's patients, suggests that cortisone has a definite effect on immune mechanisms. Whether this effect occurs at the level of antibody production, at the level of the union of antigen and antibody or at any other point in the development of the immune response is not definitely established and should prove to be an interesting problem for further study.

Summary

The effect of adrenal cortical hormones has been studied in relation to several steps in the development of immune or allergic reactions.

1. Anaphylaxis, the Arthus reaction and other manifestations of the union of antigen with antibody were not appreciably altered.

2. An anamnestic response or non-specific increase in circulating antibody was not elicited by adrenocorticotrophic hormone.

3. An inhibition of antibody production may be produced by ACTH. Further study is necessary to substantiate this finding and appraise its significance in relation to the rheumatic and other diseases thought to be related to hypersensitivity.

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